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09/770,168	02/07/01	WRIGHT D	P-4423D1

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EXAMINER	
FORMAN, J	
ART UNIT	**PAPER NUMBER**
1655	3

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/778,168	WRIGHT ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-22 are indefinite in Claim 1 for the recitation "in an isothermal nucleic acid amplification reaction" because the method does not recite method steps of isothermal amplification and therefore it is unclear how the recitation limits the method. It is suggested that Claim 1 be amended to clarify e.g. recite method steps of isothermal amplification.

b. Claims 1-22 are indefinite in Claim 1 for the recitation "a diagnostic nucleotide for the single nucleotide polymorphism about one to four nucleotides from a 3' terminal nucleotide of the detector primer" because it is unclear whether the 3' terminal nucleotide is a diagnostic nucleotide. It is suggested that the claim be amended to clarify e.g. replace "about" with "located" and replace "from" with "5' of".

c. Claims 1-22 are indefinite in Claim 1, step c), for the recitation "determining an efficiency" because "efficiency" can be either a quantitative or qualitative term both of which require definition or criteria for determining. IT is suggested that Claim 1 be amended to define "efficiency" or recite criteria for determining "efficiency".

d. Claims 2 and 3 are both indefinite in the recitation "single nucleotide polymorphism is identified" because "identified" lacks proper antecedent basis in the method of Claim 1 for "detecting a single nucleotide polymorphism". It is suggested that Claims 2 and 3 be amended to provide proper antecedent basis e.g. replace "identified" with "detected" if that is the intended limitation.

e. Claims 4 is indefinite for the recitation "two detector primers are used to identify which of two possible alleles is present in the target sequence" because both "identify" and "alleles" lack proper antecedent basis in Claim 1. It is suggested that Claim 4 be amended to provide proper antecedent basis e.g. replace "identify" with "detect" if that is the intended limitation, and replace "which of two possible alleles is present" with "the absence or presence of the single nucleotide polymorphism".

f. Claim 5 is indefinite in the recitation "identify the nucleotide present in the target sequence at the position of the single nucleotide polymorphism" because both "identify" and "the position" lack proper antecedent basis in Claim 1. It is suggested that Claim 5 be amended to provide proper antecedent basis e.g. replace "identify" with "detect" if that is the intended limitation, and replace "present in the target sequence at the position of the single nucleotide polymorphism" with "present in the single nucleotide polymorphism of the target sequence".

g. Claim 13 is indefinite in the recitation "SDA, 3SR, NASBA AND TMA" because they are abbreviations the meaning of which can change with time. It is suggested that the claim be amended to clarify e.g. "Strand Displacement Amplification (SDA)" etc.

h. Claim 17 is indefinite in the recitation "detected by mean of a label associated with the detector primer" because "associated" is a non-specific relational term and therefore the relationship between the "label" and the "primer" is undefined.

i. Claim 19 is indefinite for the recitation "fluorescence is detected as an indication of the presence of the single nucleotide polymorphism" because "indication" is a non-specific relational term and therefore the relationship between the "fluorescence" and "polymorphism" is undefined. It is suggested that the claim be amended to define the relationship e.g. replace "is an indication of" with "detects".

j. Claim 20 is indefinite for the recitation "fluorescence polarization is detected as an indication of the presence of the single nucleotide polymorphism" because "indication" is a

non-specific relational term and therefore the relationship between the "fluorescence polarization" and "polymorphism" is undefined. It is suggested that the claim be amended to define the relationship e.g. replace "is an indication of" with "detects".

k. Claim 22 is indefinite in the recitation "prior to amplifying, displacing the hybridized detector primer" because it is unclear how fits into the method of Claim 11 because it is unclear how the displaced detector primer is extended in step b). It is suggested that Claim 22 be amended to clarify e.g. recite method steps of hybridizing, extending, displacing, and amplifying.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-5, 7-12, 14-18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42).

Regarding Claim 1, Newton et al. disclose a method for detecting a single nucleotide polymorphism in a target comprising: hybridizing a detector primer to the target, wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism and is complementary to the target sequence; amplifying the target by hybridization and extension of the detector primer (Column 4, lines 31-67); determining efficiency of the detector primer extension; and detecting the presence or absence of the single nucleotide polymorphism based

on the efficiency of the detector primer extension (Column 13, lines 11-34) wherein the amplification reaction is an isothermal reaction i.e. performed at the melting temperature of the sequence (Column 7, lines 50-60) and wherein the diagnostic nucleotide is a terminal nucleotide complementary to the polymorphism (Column 4, lines 35-37) but they do not teach the diagnostic nucleotide is about one to four nucleotides from a 3' terminal nucleotide. However, diagnostic nucleotides adjacent to the 3' terminal nucleotide were well known in the art at the time the claimed invention was made as taught by Reynolds et al. and Krausa et al. Specifically, Reynolds et al. teach a similar method for detecting a single nucleotide polymorphism in a target sequence comprising: hybridizing a detector primer comprising a diagnostic nucleotide to the target; amplifying the target and detecting the presence or absence of the single nucleotide polymorphism, wherein the amplification reaction is an isothermal amplification reaction (Column 3, lines 17-45 and Column 11, lines 5-20 and Column 12, lines 59-67) and wherein the diagnostic nucleotide is near the 3' end of the terminal nucleotide (Column 11, lines 11-16). Additionally, Krausa et al. teach diagnostic primer comprising a diagnostic nucleotide about one to four nucleotides from the 3' end wherein the primers identify polymorphic sites and provide for fine mapping of polymorphisms (page 38, left column, lines 8-20). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the teaching of Reynolds et al. wherein the diagnostic primer is near the 3' end of the terminal nucleotide of the diagnostic primer to the terminal nucleotide diagnostic primers of Newton et al. to provide diagnostic primers having a diagnostic nucleotide about one to four nucleotides from the 3' terminal nucleotide of the diagnostic primer based on the known location of a polymorphism as taught by Krausa et al. for the obvious benefit of polymorphism-specific detection and complete polymorphism mapping as taught by Krausa et al. (page 38, left column, lines 8-20).

Regarding Claim 2, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using the detector primer i.e. the primer is extended only when the terminal nucleotide of the primer is complementary to the target (Column 12, lines 47-59).

Regarding Claim 3, Newton et al. teach the method wherein the single nucleotide polymorphism is identified using two or more detector primers comprising different diagnostic nucleotides (Column 30, Example 1).

Regarding Claim 4, Newton et al. teach the method wherein two detector primers are used to identify which of two possible alleles is present in the target sequence (Column 30, Example 1).

Regarding Claim 5, Newton et al. teach the method wherein four detector primers are used to identify the nucleotide present in the target sequence at the position of the single nucleotide polymorphism (Column 32, Example 4).

Regarding Claim 7, Newton et al. teach the method wherein the detector primer further comprises a nucleotide which forma a nondiagnostic mismatch with the target sequence (Column 12, lines 22-26).

Regarding Claim 8, Newton et al. teach the method wherein the nodiagnostic nucleotide is positioned within fifteen nucleotides of the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 9, Newton et al. teach the method wherein the nodiagnostic nucleotide is positioned 1-5 nucleotides from the diagnostic nucleotide in the detector primer (Column 12, lines 27-32).

Regarding Claim 10, Newton et al. teach the method wherein the nodiagnostic nucleotide adjacent to the diagnostic nucleotide in the detector primer i.e. 1, 2 or 3 bases from the terminal nucleotide (Column 12, lines 27-32).

Regarding Claim 11, Newton et al. teach the method wherein the detector primer is about 15-36 nucleotides long (Column 11, lines 12-20).

Regarding Claim 12, Newton et al. teach the method wherein the detector primer is about 18-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 14, Newton et al. teach the method wherein the detector primer is about 12-50 nucleotides long (Column 11, lines 12-20).

Regarding Claim 15, Newton et al. teach the method wherein the detector primer is about 12-24 nucleotides long (Column 11, lines 12-20).

Regarding Claim 16, Newton et al. teach the method wherein the detector primer is about 12-19 nucleotides long (Column 11, lines 12-20).

Regarding Claim 17, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer (Column 14, lines 40-48).

Regarding Claim 18, Newton et al. teach the method wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23).

Regarding Claim 21, Newton et al. teach the method wherein the efficiency of detector primer extension is determined quantitatively i.e. detection of heterozygous or homozygous samples (Column 13, lines 35-41).

5. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Mullis et al. (U.S. Patent No. 4,683,195, issued 28 July 1987).

Regarding Claim 6, Newton et al. teach the method wherein the detector primer has a 5' tail sequence (Column 11, lines 40-45) but they do not teach each of the multiple primers has a different 5' sequence. Reynolds et al. teach the similar method wherein the detector primer

has a 5' tail sequence wherein the 5' tail sequence facilitates cloning and sequencing as taught by Mullis et al. (Column 11, lines 21-27) and Mullis et al. teach multiple primers comprise a different 5' tail sequence to facilitate cloning and sequencing of individual amplified products (Column 15, lines 38-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' tail sequence of the detector primers taught by Newton et al. and Reynolds to provide each detector primer with a different 5' tail sequence for the expected benefit of facilitating cloning and sequencing of individual amplified products as taught by Mullis et al. (Column 15, lines 38-47) to thereby simplify identification of individual single nucleotide polymorphic loci.

6. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Guatelli et al. (Proc. Natl. Acad. Sci. USA, 1990, 87: 1874-1878).

Regarding Claim 13, Newton et al. teach the method is an isothermal amplification reaction (Column 7, lines 50-60) but they do not teach the reaction is selected from SDA, 3SR, NASBA and TMA. Reynolds et al. teach the similar method comprising 3SR amplification (Column 12, lines 59-67). Additionally, Guatelli et al. teach 3SR amplification and motivation for applying 3SR amplification in target detection i.e. 3SR amplification produces ten-million fold amplification in less than two hours which is useful for detecting targets of low abundance (Abstract). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the 3SR amplification of Reynolds et al. to the similar

isothermal amplification of Newton et al. for the expected benefits of detecting rare or low copy number target sequences as taught by Guatelli et al. (Abstract).

7. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Chen et al. (Nucleic Acids Research, 1997, 25(2): 347-353).

Regarding Claims 19 and 20, Newton et al. teach the method wherein the presence or absence of the single nucleotide polymorphism is detected by means of a label associated with the detector primer, wherein the label becomes detectable upon extension of the detector primer (Column 8, lines 13-23) but they do not teach the label is a fluorescent donor/quencher dye pair (Claim 19) and they do not teach a change in fluorescence is detected as an indication of the presence of the single nucleotide polymorphism (Claim 20). However, Chen et al. teach a similar method for detecting a single nucleotide polymorphism comprising hybridizing a detector primer to the target; amplifying the target by extension of the detector primer; and detecting the single nucleotide polymorphism and wherein the single nucleotide polymorphism is detected by a label associated with the detector primer, wherein the label produces a change in signal upon extension of the detector primer and wherein the label is a fluorescent donor/quencher pair and a decrease in donor dye (page 348, right column, first and second full paragraphs). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fluorescence donor/quencher dye pair of Chen et al. wherein a change in fluorescence determines the presence of the single nucleotide polymorphism to the fluorescence detection of single nucleotide polymorphism of Newton et al.

for the expected benefits of highly sensitive and specific detection of primer extension product as taught by Chen et al. (page 348. right column, second full paragraph).

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (U.S. Patent No. 5,595,890, issued 21 January 1997) in view of Reynolds et al. (U.S. Patent No. 5,763,184, issued 9 June 1998) and Krausa et al. (Human Immunology, 1995, 44: 35-42) as applied to Claim 1 above and further in view of Walker et al. (Nucleic Acids Research, 1992, 20(7): 1691-1696).

Regarding Claim 22, Newton et al. do not teach the method wherein prior to amplifying, the detector primer is displaced from the target by extension of an upstream primer. However, Strand Displacement Amplification was well known in the are at the time the claimed invention was made as taught by Walker et al. Specifically, Walker et al. teach hybridizing a detector primer to a target, displacing the detector primer from the target by extension of an upstream primer and amplifying the target (page 1692, Fig. 1) wherein displacement generates target sequence of defined 3' and 5' ends with increased efficiency and decreased non-specific primer binding (Abstract). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the amplification of Newton et al. by extending an upstream primer to displace the detector primer prior to amplification of the target sequence for the expected benefits of increased efficiency and decreased non-specific product formation as taught by Walker et al. (Abstract) to thereby efficiently and accurately detect a single nucleotide polymorphism.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
June 28, 2001

SUPERVISORY PATENT EXAMINER
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